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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,883	08/25/2005	Jorg Peters	Le A 36 075	7044

35969 7590 08/27/2009

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EXAMINER	
LI, RUIXIANG	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
08/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,883	PETERS ET AL.	
	Examiner	Art Unit	
	RUIXIANG LI	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 19* is/are pending in the application.

4a) Of the above claim(s) *18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/03/2009 has been entered. Claims 1-19 are pending. Claims 1-17 and 19 are under consideration. Claim 18, which is drawn to a distinct invention from the invention group being examined, is withdrawn from further consideration

Withdrawn Objections and/or Rejections

2. The rejections of claims 3 and 10 under 35 U.S.C. §112, second paragraph are withdrawn in view of amended claims.

Claim Rejections Under 35 U.S.C. §103 (a)

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-6, 8, 11, 13, 14, 17, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) in view of Wyllie et al. (U.S. Patent No. 5,932,102, Aug. 3, 1999).

Domingues et al. teach a method for purifying interleukin-4 or mutants by recombinant expression comprising (a) expression in inclusion bodies (page 220, right column, the 3rd paragraph), (b) disrupting the cells and separating the inclusion bodies, (c) washing inclusion bodies obtained with 0.1 M Tris-HCl pH8/1 mM EDTA/0.1% zwittergent, (d) solublizing the inclusion bodies in 8 M GdnHCl, (e) renaturating the expression product and purifying the expression product by cross-flow ultrafiltration against five volumes of buffer (page 220, right column, the 4th paragraph to page 221, the first paragraph of left column).

Domingues et al. fail to teach steps (e) and (f) of claim 1, .i.e., separating the denatured IL-4 or muteins thereof using an immobilized metal chelate affinity chromatography (IMAC) system and releasing the IL-4 or muteins thereof from the IMAC system.

Wyllie et al. teach a method for purifying a protein containing histidine residues using immobilized metal affinity chromatography (Abstract). Wyllie et al. teach that human IL-4 has 5 histidine residues and is predicted to have high affinity to the immobilized metal (bottom of column 3). Wyllie et al. also teach purifying human IL-4 from E. coli. using Zinc-chelating affinity chromatography (columns 5 to 6).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Domingues et al. to purify

the denatured IL-4 or muteins thereof using an immobilized metal chelate affinity chromatography with a reasonable expectation of success. One would have been motivated to do so because an immobilized metal chelate affinity chromatography provides an alternative approach for purifying IL-4 as demonstrated by Wyllie et al. The purity of interleukin-4 or mutants thereof purified using Zinc-chelating affinity chromatography would necessarily have a purity of about 90% as estimated by SDS-PAGE analysis.

It is also noted that while the cited references do not teach the specific zwitterionic detergents listed in claim 19, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use a zwitterionic detergent, such as CHAPS or zwittergent series, in a washing buffer with a reasonable expectation of success. One would have been motivated to do so because a zwitterionic detergent, such as CHAPS or zwittergent series,has been widely used for such a purpose.

5. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) and Wyllie et al. (U.S. Patent No. 5,932,102, Aug. 3, 1999) as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above, and further in view of Apeler et al. (EP 1022337 A2, 07/26/2000).

Domingues et al. and Wyllie et al. teach a method for purifying interleukin-4 or mutants by recombinant expression using an immobilized metal chelate affinity chromatography as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above.

Domingues et al. and Wyllie et al. fail to teach a method for purifying an interleukin-4 mutant, Interleukin-4 R121D Y124D.

Apeler et al. teach expression of a human interleukin-4 mutant, Interleukin-4 R121D Y124D (page 2, paragraphs [0002] and [0007]).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the method taught by Domingues et al. and Wyllie et al. to purify interleukin-4 R121D Y124D using an immobilized metal chelate affinity chromatography with a reasonable expectation of success. One would have been motivated to do so because the human interleukin-4 mutants, Interleukin-4 R121D Y124D, comprise 5 histidine residues and would have high affinity to an immobilized metal as taught by Wyllie et al. (bottom of column 3).

6. Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) and Wyllie et al. (U.S. Patent No. 5,932,102, Aug. 3, 1999) as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above, and further in view of Apeler et al. (EP 1022337 A2, 07/26/2000).

Domingues et al. and Wyllie et al. teach a method for purifying interleukin-4 or mutants by recombinant expression using an immobilized metal chelate affinity chromatography as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above.

Domingues et al. and Wyllie et al. fail to teach the renaturation of interleukin-4 or mutants by dialysis in the presence of an artificial chaperone.

Gellman et al. teach the use of an artificial chaperone, such as β-cyclodextrin for refolding enzymes (see Example 1).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Domingues et al. and Wyllie et al. to use an artificial chaperone, such as β-cyclodextrin for refolding interleukin-4 or mutants thereof with a reasonable expectation of success. One would have been motivated to do so because an artificial chaperone, such as β-cyclodextrin, causes the detergents to be sequestered from a protein and detergent complex and allows the protein to achieve the correct folding as demonstrated by Gellman et al. (see, e.g, Example 1).

7. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) and Wyllie et al. (U.S. Patent No. 5,932,102, Aug. 3, 1999) as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above, and further in view of Bonsch et al. (J. Biol. Chem. 270:8452-8457, 1995).

Domingues et al. and Wyllie et al. teach a method for purifying interleukin-4 or mutants by recombinant expression using an immobilized metal chelate affinity chromatography as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above.

Domingues et al. and Wyllie et al. fail to teach a method for purifying mIL-4 Q116D and Y119D.

Bonsch et al. teach mIL-4 Q116D and Y119D, the murine homologs of human IL-4 R121D and Y124D (Fig. 8; page 8457, right column).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the method taught by Domingues et al. and Wyllie et al. to purify mIL-4 Q116D and Y119D using an immobilized metal chelate

affinity chromatography with a reasonable expectation of success. One would have been motivated to do so because mIL-4 Q116D and Y119D, the murine homologs of human IL-4 R121D and Y124D, comprise histidine residues and would have high affinity to an immobilized metal as taught by Wyllie et al. (bottom of column 3).

8. Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) and Wyllie et al. (U.S. Patent No. 5,932,102, Aug. 3, 1999) as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above, and further in view of US Patent No. 5,739,281 (Apr. 14, 1998).

Domingues et al. and Wyllie et al. teach a method for purifying interleukin-4 or mutants by recombinant expression using an immobilized metal chelate affinity chromatography as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above.

Domingues et al. and Wyllie et al. fail to teach renaturing the denatured IL-4 or muteins thereof prior to step (f) by matrix-assisted refolding.

US Patent No. 5,739,281 teaches refolding of numerous proteins, including human and murine β2-microglobulin (Example 1) and human growth hormone (Example 2) by a cyclic folding procedure on Ni^{2+} activated NTA-agarose matrix (Ni^{2+}NTA-agarose).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Domingues et al. and Wyllie et al. to use matrix-assisted refolding taught by US Patent No. 5,739,281 wherein the IL-4 remains bound to the IMAC system with a reasonable expectation of success. One would have been motivated to do so because matrix-assisted refolding provides

an efficient and alternative approach for refolding of proteins as demonstrated by US Patent No. 5,739,281.

9. Response to Applicants' argument

Applicants argue that Wyllie et al. is concerned with the purification of fully natured, native proteins from crude cell extract that have not been treated with any denaturing agent. Applicants argue that does not teach, suggest or even mention denatured IL-4 or denatured proteins generally. Applicants argue that Wyllie et al. does not teach or suggest separating denatured IL-4 or any protein on an IMAC system. Applicants argue that Wyllie et al. teach that histidine availability is not simply proportional to the total number of His residues in a protein and that the total number of His residues does not solely determine affinity to IMAC. Applicants argue that the method of Wyllie et al. correlates certain tertiary structure information and primary sequence information of a protein of interest against the relative affinity of that protein of interest for IMAC resin. Applicants argue that the method of Wyllie et al. is not a suitable tool of predictability for the affinity of denatured proteins for IMAC resins. Applicants argue that one of ordinary skill in the art would not have had any reasonably expectation of success in view of Wyllie et al. to achieve the present invention.

Applicants' argument has been fully considered, but is not deemed to be persuasive for the following reasons.

Wyllie et al. teach a method for purifying a protein containing histidine residues using immobilized metal affinity chromatography (Abstract). The method comprises

(a) sequencing the protein and determining if the protein contains one or more histidine residues; (b) determining the hydrophilic index (HI) of the histidine residues of said protein; (c) adjusting the pH of the solution containing the protein is adjusted to about 6.75 to 7.2 if the HI of at least one of the histidine residue is at least 2; (d) applying the solution to an IMAC column so that the protein binds to the column (claim 1). In particular, Wyllie et al. teach that human IL-4 has 5 histidine residues and is predicted to have high affinity to the immobilized metal (bottom of column 3). The 5 histidine residues of hIL-4 have predicted HIof 2.03, 1.87, 2.77, 2.71, and 1.65, respectively (bottom of column 3).

In view of the teachings of Wyllie et al., it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Domingues et al. to purify the denatured IL-4 or muteins thereof using an immobilized metal chelate affinity chromatography with a reasonable expectation of success. One would have been motivated to do so because the teachings are not limited to fully natured, native proteins as applicants have argued. From the teachings of Wyllie et al., one of skill in the art would have understood that as long as the HI of at least one of the histidine residue of a protein was at least 2, the protein would bind to an IMAC column.

Conclusion

10. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

/Ruixiang Li/
Primary Examiner, Art Unit 1646

Ruixiang Li, Ph.D.
August 25, 2009